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(54) TABLETS

(71) We, BOEHRINGER INGELHEIM G.m.b.H, a German Body Corporate of Ingleheim am Rhein, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to coated sustained release tablets.

Numerous pharmaceutical substances are quickly absorbed in the gastro-intestinal tract of humans and of animals and, subsequently, quickly eliminated. This means that the action of such pharmaceutical substances is in general only of short duration.

In order to ensure that the activity of a pharmaceutical substance extends over a long period and to avoid the necessity of repeatedly taking tablets within short time intervals, tablets with sustained release have been developed. These are characterised by releasing the pharmaceutical substance only slowly while passing through the patient's gastro-intestinal tract. It would be ideal if for the production of such susained release forms the differing degrees of absorption in the several sections of the gastro-intestinal tract could be taken into consideration. As the degree of absorption taking place within a particular section of the gastro-intestinal tract depends among other things upon the speed of passage of the pharmaceutical substance through the tract and the surface as well as numerous permeability criteria, it is understandable that not all these factors can be observed. For this as well as technological reasons concerning the large scale production of such sustained release forms, the production has been restricted to sustained release forms which simply release the active ingredient gradually over a long period of time.

In this connection, sustained release forms have for example been known containing the active ingredient within a structure containing an insoluble substance. The active ingredient can thus be covered on both sides with a layer of the insoluble substance (see for example Austrian Patent No. 205,671). As indicated in the Austrian Patent and confirmed by trials, constant release of the active ingredient per unit time is not achieved. The sustained release shows rather an exponential decrease with time. This is readily understood when one bears in mind that the tablet surface coming into contact with its environment becomes continuously smaller.

Another form of table, developed with the aim of obtaining a homogeneous release of substance per unit time over a period of several hours, has been described in U.S. Patent No. 3,146,169 and in the corresponding German Patent No. 1,298,238. In this case a tablet core comprising the active ingredient is covered with an insoluble and indigestible coat by means of pressure coating, and a circular hole is formed at one place in the tablet. As described therein, and proved by *in vitro* trials, a release of active ingredient takes place through this hole such that in equal periods of time equal quantities of substance dissolve and are therefore available for absorption. This means, that the cumulative release of active ingredient increases linearly with time. This form of sustained release, however, is only useful for active ingredients absorbed to an equal extent in each of the various intestinal sections.

There are numerous substances the absorption of which clearly decreases during their passage through the gastro-intestinal tract, and which, starting from the stomach, are absorbed less and less in the small intestine, the farther through they go.

In order to obtain a constant pharma-

cological effect over a long period of time for such active ingredients, the decreasing absorption in the lower sections of th intestine must be compensated by an increased release of active ingredients, i.e. the release of active ingredient must increase continuously with time. This means that the active ingredient, released within a certain period of time, increases exponentially with increasing time.

An object of the present invention is thus to provide sustained release tablets (i.e. tablets which provide sustained release of a pharmaceutical substance during passage through the gastro-intestinal tract) which show an exponentially increasing release of pharmaceutical substances as the tablets pass through the gastro-intestinal tract.

According to the present invention there is provided a sustained release tablet which comprises at least one substantially spherical core comprising the active ingredient in a form readily releasable in the gastro-intestinal tract and a coating of an insoluble and indigestible substance, at least one hole being provided in the said coating through which the said active ingredient can be released during the passage of the tablet through the gastro-intestinal tract, the said hole being either uncovered or covered by a layer of active ingredient.

The coated sustained release tablets advantageously include one or two substantially spherical active ingredient cores. The hole in the coat, which is preferably round, makes possible the release of dissolved material from the active ingredient core. The tablet coat is preferably made of a material, which, in the fluids of the human and animal gastro-intestinal tract, remains insoluble, indigestible, incapable of absorption and essentially impenetrable by the active ingredient. Preferably, the coated tablet keeps its shape for a considerable period of time, e.g. at least for 6 hours and softens only for excretion with the content of the large intestine.

In the case of tablets with cylindrical cores containing the active ingredient provided with an insoluble and indigestible coating and with a hole drilled partly or completely through the tablet, it has been found that the quantity of active ingredient released increases only linearly as the tablet passes through the gastro-intestinal tract. In contrast with the tablets according to the present invention, the quantity of active ingredient released can be made to increase approximately exponentially.

It is believed that this phenomenon can be explained by the differences in the way that the active ingredient is dissolved from the core. With a cylindrical core having a hole therethrough, the active ingredient is dissolved outwards from the hole. With a rounded core, on the other hand, the region in which the active ingredient is dissolved can spread outwards in an approximately spherical or orbicular form, and the nearer the spreading region of dissolution comes to a spherical form the nearer the rate of dissolution of active ingredient will come to being a function of the second power of the radius of the said region.

In order to produce coated sustained release tablets according to the invention, one may, for example, proceed either according to the pressure coating process (whereby the holes will be formed in the coating only) or one may form coated tablets in conventional manner and then provide one or more holes by drilling. The procedure of drilling has the special advantage that the active ingredient core may also be penetrated to any desired extent. The rate of release of active ingredient per unit time depends, not only on the solubility of the active ingredient portion, but also on the diameter and depth of the drilled hole. By varying the diameter and depth of the drilled hole, the desired degree of medicament release (increasing exponentially with time) may be determined by simple trials and adjusted as desired.

Any suitable pharmaceutical substance may be used as the active ingredient, which substance may be molded to form the substantially spherical cores with or without excipients according to the principles of galenic technology. Plastics, lacquers or other materials, which are mainly insoluble, indigestible, nonabsorbable, impermeable for the included medicament and which do not splinter when being drilled may conveniently be used as the coating for the core.

In the production of such sustained release tablets, it is also possible to fill or seal partly or completely the drilled hole by applying an additional coating containing active ingredient around the whole coated tablet, the said additional coating being capable of releasing the active ingredient contained therein upon entering into the gastro-intestinal tract.

In Figures I, II, III and IV, four types of coated tablets according to the invention are shown in cross section and as seen from above. Figure 1 shows a core (a) containing active ingredient, covered by an insoluble coat (b), which has a circular cavity (c). The medicament can flow out of this cavity. Figure II shows a similar coated tablet, the active ingredient core (a) and insoluble coat (b) being drilled in such a way that the hole (c) reaches to the middle of the active ingredient core. Figure III showsa similar coated tablet, around which has been applied, however, an additional coating containing active ingredient, thus

sealing the drill hole (d). This coating containing active ingredient dissolves first and, thus, makes availabl , for example in the stomach active ingredient for initial absorption. During the passage of the substance through the intestines, the release of active ingredient increases exponentially with time. Figure IV shows two active ingredient cores (a) covered by an insoluble coating (b), into which cores holes have been drilled from both ends (c). The final tablet is in cylindrical form, semispherical at both ends, and is formed by filling the space between the two adjacent cores with inert material.

For experimental examination of the coating tablets produced according to the invention, the following tests were carried out: spherical coating tablets, (containing besides the filler (glucose 64.8%, powdered sugar 31.6%, stearic acid 2.6%) 1% of the dyestuff Evans Blue) the surfaces of which were covered by an insoluble layer of lacquer, were drilled either according to the embodiment shown in Figure I, on one side in order to penetrate the insoluble coat, or according to the embodiment shown in Figure II, from one side through the coat to the middle of the tablet core. The dissolving properties of the coated tablet were examined at a constant temperature (37° ± 1°C) in an agitator. The coated tablets which had been weighed before dissolving tests, were taken out of the agitator after various periods of time, dried, weighed, then completely dissolved, dried again and the weight of the insoluble coat determined. From the difference in weight the percentage proportion of dissolved material was determined in each case. Additionally the percentage proportion of the dyestuff concentration was determined in respect of each coating table which had dissolved in the solution. For each test period, 5 coated tablets each in individual containers were used and average values were found from the decrease in weight measurement as well as the dyestuff determination. The differences in the average values, obtained from both methods, for the percentage portion which had dissolved, was very low, i.e. ± 2% at the most.

Experiments which have been carried out to test the properties of the sustained release tablets according to the invention are described below with reference to Figs. VII to XII of the accompanying drawings. These drawings, which are referred to in detail below, illustrate the following:

Fig. VII The dissolving properties of coated tablets drilled to the middle (Row A) and on the surface (Row B) are compared. It can be seen that dissolution of the coated tablets drilled to the middle takes place more rapidly and in a more "spherical" or "orbicular" form than in the case of the coated tablets drilled only on the surface.

Fig. VIII The accumulated dissolution of three different coated tablets dependent upon time is compared graphically. Th tables are A (hole diameter = 3 mm, drilled to centre of tablet), B (hole diameter = 2 mm, drilled to centre) and C (hole only on surface). In all three cases, the release of active ingredient increases exponentially with time.

Fig. IX The dissolved quantities per unit time depending on time are compared graphically for the tablets A, B and C described above with reference to Fig. VIII. The values are expressed as percentages of the total quantity of coated tablet and are taken from Fig. VIII. It is evident that the quantities released per unit time increase exponentialy in all three cases.

Fig. X For the purposes of comparison, the accumulated dissolution dependent upon time are compared graphically for the tests described in United States Patent No. 3,146,169 (values from Table 1 thereof). In all cases, the release increases substantially linearly with time.

Fig. XI Again for the purposes of comparison, dissolved quantities per unit time depending on time are compared graphically for the tests described in United States Patent No. 3,146,169. It is clear that the quantities released per unit time differ greatly one from another, except in the case of curves a and b. They do not increase linearly or exponentially in any case.

Fig. XII The accumulated dissolution of coated tablets depending on time is compared graphically for the two tablets A (as illustrated in Fig. V) and B (as illustrated in Fig. VI). In both cases release of active ingredient increases linearly with time.

In preliminary tests with coated tablets as shown in Figures I and II, the dissolving properties illustrated diagrammatically in Figure VII were observed after cutting the dried coated tablets. It is to be recognised that with the coated tablets drilled up to the middle (row A) comparatively quick and almost spherical-shaped dissolution takes place. In the case of the coated tablets the insoluble coat of which had only been drilled slightly (row B), the dissolving process is slower and in a more semispherical shape as expected. In addition to these subjective observations, the results of the objective measurements on the dissolving properties illustrated in Figure VIII show that coated tablets drilled up to the middle (curve A, diameter of hole 3mm and curve B, diameter of hole 2 mm) as well as coated tablets drilled only superficially in order to remove the insoluble coat (curve C), dissolve in an exponential manner depending upon time. The measured values

indicated in Figure VIII represent the average values of the weight determinations and concentration measurements of each group of 5 coated tablets. The quicker dissolution of the coated tablets, apparent from curve A in comparison with curve B, is affected by the size of the drilled hole, with the former hole having a larger diameter (3 mm) while the latter hole has a smaller diameter (2 mm). Corresponding statements hold true for curve C, where the coated tablets used were only slightly drilled in order to make a hole in the insoluble coat. The exponential dissolving properties are clear in each case. In general they extend to a range of up to approx. 80% of the total mass of the coated tablet. These results show, that the degree of exponential release may be varied by the diameter as well as by the depth of the drilled hole. Additionally it is, of course, possible to achieve variations of release in total time by changes in the composition of the compressed tablet core or by the variation of other galenic parameters. Furthermore, it is obvious for example that in order to double the released quantity of substance per unit time two cores can be combined to provide a tablet in the form of a cylinder with semispherical ends corresponding to Figure IV. In general, these tests show that by means of the principle described above it is basically practicable to obtain any exponentially increasing release property within a given time as desired.

When comparing the coated sustained release tablets described here with the tablets described in U.S. Patent 3,146,169, the first important difference which must be stressed is that the sustained release forms described here include substantially spherical cores while the tablets described in the U.S. Patent represent flat-cylindrical forms or three-dimensional arrangements closely resembling cylindrical form. The only factors which the coated retard tables according to the invention and the type of tablets described in the U.S. Patent have in common is that the core containing the active ingredient is covered with a coat essentially insoluble in the gastro-intestinal tract, and that both forms of the tablets have a hole, through which the active ingredient from the core may escape for absorption in the gastro-intestinal tract. The above-mentioned fundamental difference in the three-dimensional arrangements of the two forms is, simultaneously, the basis of the differing time dependent release properties. A comparison of the experiments on the tablets of the present invention herein described with the test results mentioned in the U.S. Patent, in particular, for the values for the time dependent release properties shown in Tables I and II further confirms the difference between both processes. The values in Tables I and II of the U.S. Patent show, as may be seen, clearly from Figure IX an almost linear curve, when adding up the quantities dissolved in the individual test periods. This has been further confirmed by tests of our own, with tablets, i.e. with flat cylindrical bodies, which had been drilled on one side corresponding to Figure V, or as shown in Figures VI, through the centre of their largest surface, Figure XII shows clear linear release properties for tablets slightly drilled on one side (curve A) as well as for the drilled through tablets (curve B). The readings for Figure X were obtained in the same way as for the tablets of the present invention.

However, if one considers in comparison thereto the most important dissolution per test period depending on time of the tablets of the present invention as well as of the tablets described in the U.S. Patent besides the accumulated values in Figures VIII and X for time dependent release results as presented in Figure IX and Figure XI are obtained. The values in Figure IX are derived from curves A, B and C of Figure VIII and the values in Figure XI are similarly obtained from the curves a to e in Figure X. A comparison of the results presented in Figure VIII and Figure IX shows for the tested tablets of the present invention, that the quantity of substance released per unit time increases exponentially wth the time. Compared to this, the comparison of Figure X with Figure XI shows, that in the trials based on the U.S. Patent (corresponding to the statement made therein) the quantity of substance released per unit time at best remains constant with time. Thus, the decisive comparison between the curves of Figure IX and those of Figure XI proves the fundamental difference in release properties between the tablets of the present invention and the cylindrical tablets described in the U.S. Patent.

WHAT WE CLAIM IS:—

1. A sustained release tablet which comprises at least one substantially spherical core comprising the active ingredient in a form readily releasable in the gastro-intestinal tract and a coating of an insoluble and indigestible substance, at least one hole being provided in the said coating through which the said active ingredient can be released during the passage of the tablet through the gastro-intestinal tract, the said hole being either uncovered or covered by a layer of active ingredient.

2. A sustained release tablet as claimed in claim 1, in which two rounded cores are coated with the insoluble and indigestible substance whereby the tablet is cylindrically shaped with rounded ends.

3. A sustained release tablet as claimed in claim 2, wherein at least one hole is provided in the said coating for each of the two cores.

4. A sustained release tablet as claimed in any of the preceding claims wherein the hole or holes extend into the active ingredient core(s).

5. A sustained release tablet as claimed in any of the preceding claims wherein the insoluble and indigestible coating is surrounded by a further coating containing active ingredient in a form readily releasable in the gastro-intestinal tract.

6. A sustained release tablet as claimed in claim 5 wherein the said further coating at least in part fills the hole or holes.

7. A sustained release tablet as claimed in claim 1 substantially as herein described.

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1372040 COMPLETE SPECIFICATION
4 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

FIG. I.

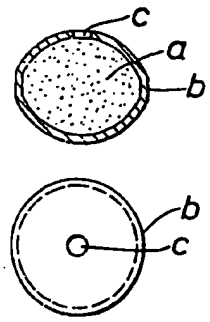


FIG. II.

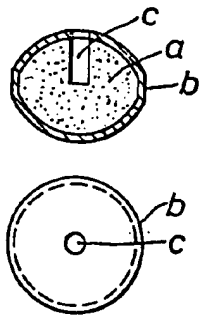


FIG. III.

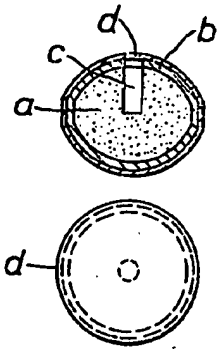


FIG. IV.

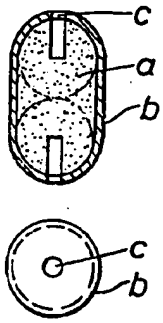


FIG. V.

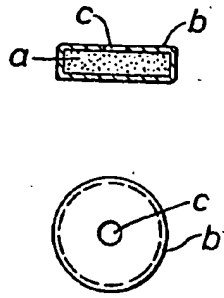


FIG. VI.

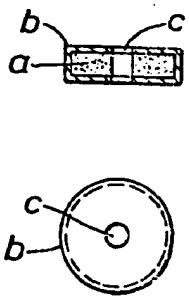


FIG. VII.

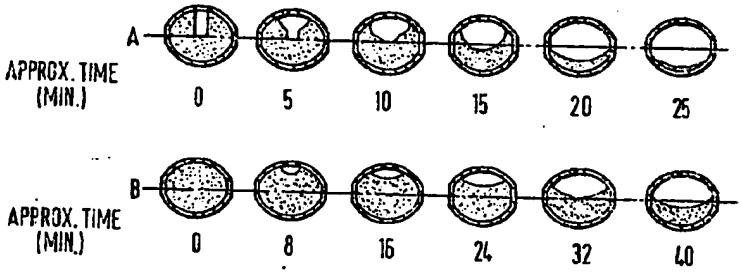


FIG. VIII.

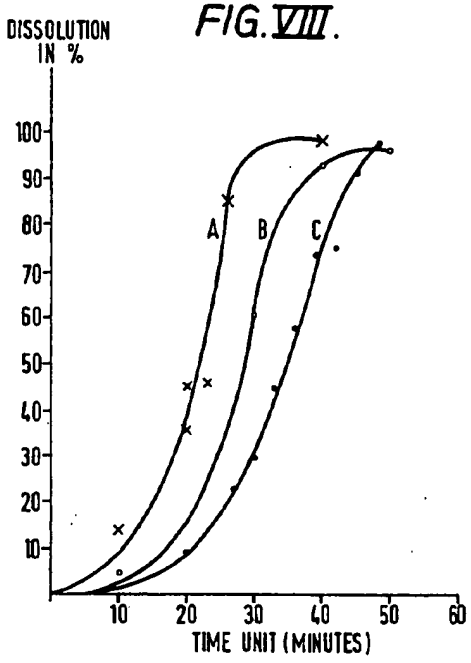


FIG. XII.

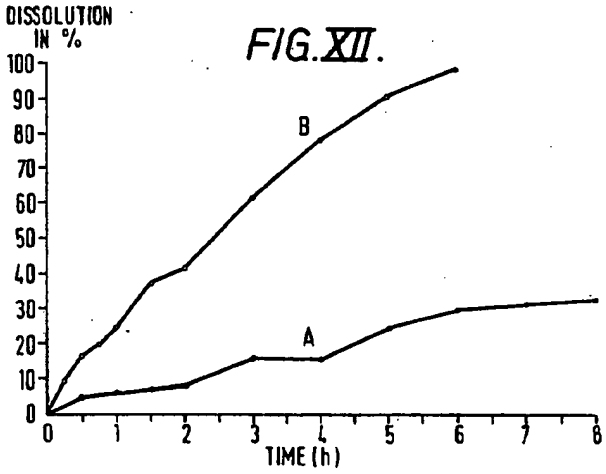


FIG. IX.

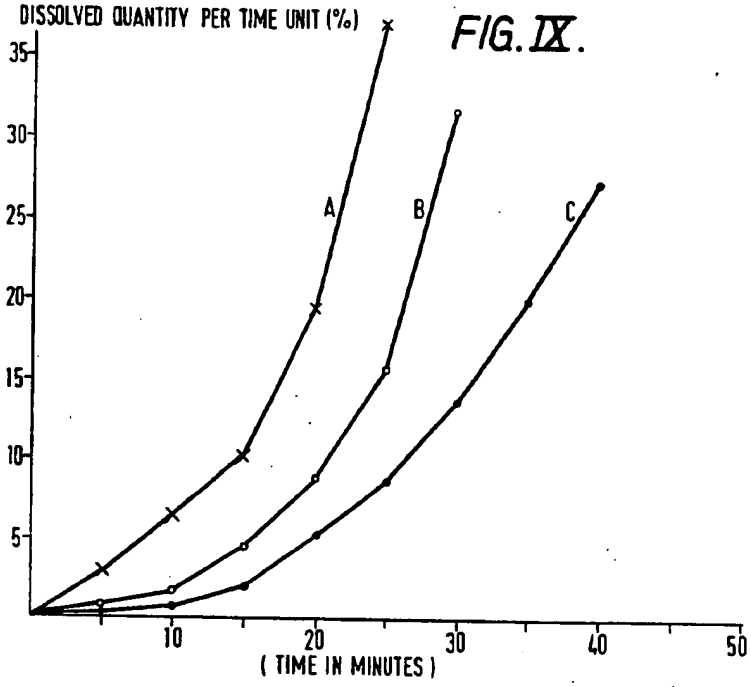

DISSOLVED QUANTITY PER TIME UNIT (%)
35
30
25
20
15
10
5
A
B
C
10
20
30
40
50
(TIME IN MINUTES)

FIG. X.

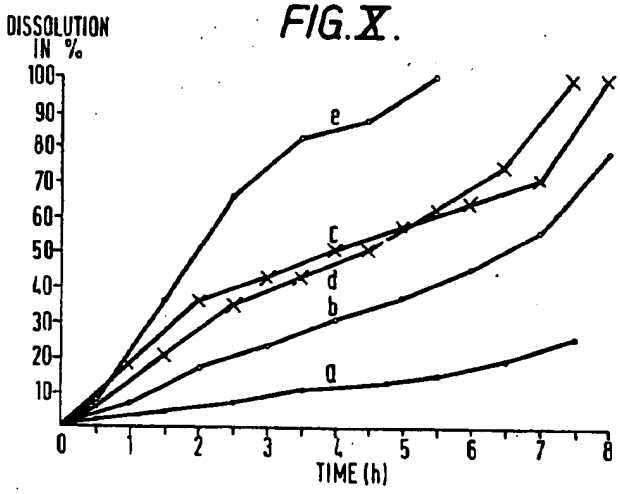
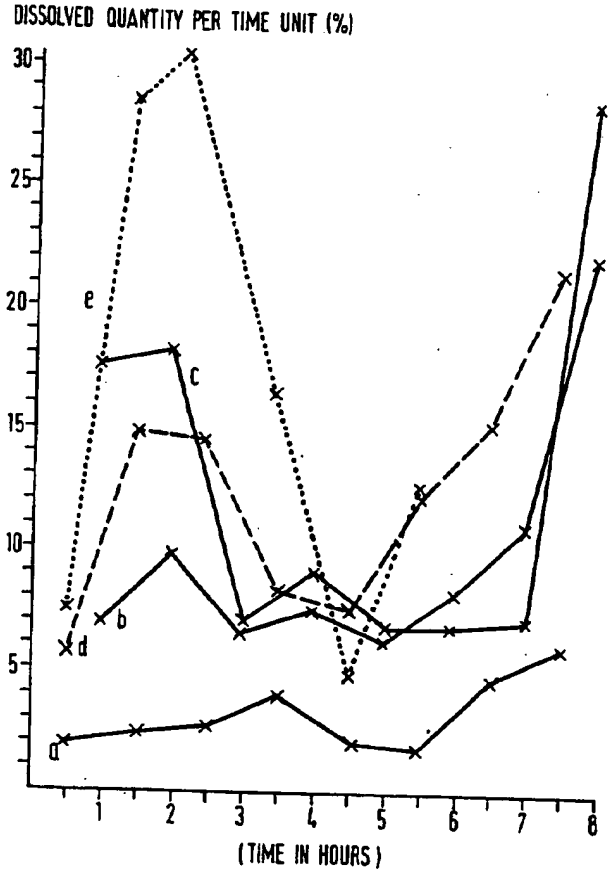

DISSOLUTION IN %
100
90
80
70
60
50
40
30
20
10
e
c
d
b
a
0
1
2
3
4
5
6
7
8
TIME (h)

FIG. XI.


DISSOLVED QUANTITY PER TIME UNIT (%)
30
25
20
15
10
5
e
c
b
d
a
1
2
3
4
5
6
7
8
(TIME IN HOURS)